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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/669,390	09/24/2003	Stephen B. Roscoe	58625US002	3951

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EXAMINER	
NEGIN, RUSSELL SCOTT	

ART UNIT	PAPER NUMBER
1631	

NOTIFICATION DATE	DELIVERY MODE
10/10/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/669,390	ROSCOE ET AL.	
	Examiner	Art Unit	
	Russell S. Negin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Comments

Applicants' amendments and request for reconsideration in the communication filed on 12 July 2007 are acknowledged and the amendments are entered.

Claims 1-25 are pending, and claims 1-24 are examined in this Office action.

Claim Rejections - 35 USC § 112

The following rejections are necessitated by amendments of applicant on 12 July 2007:

Claims 1-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the phrase "consist of at least" in line 3. While "consist" parameters must only be what is stated (closed language), at least signifies open language. Thus, it is unclear as to whether this claim is interpreted to have open or closed language.

Claim 1, line 7; claim 6, line 1; claim 7, lines 1-2; and claim 9, lines 1-2 recite the limitation "at least one model compound." There is insufficient antecedent basis for this limitation in the claim. It is unclear whether this recitation of "at least one model compound" refers to the model compound recited in line 4 of claim 1 or a different model compound.

Claim 1 recites the limitation "a model compound of at least one model compound-excipient formulation" in lines 10-11. There is insufficient antecedent basis for this limitation in the claim. It is unclear whether this recitation of a model compound is the same as what is provided in the "providing" step (lines 7-8 of claim 1), or a different model compound.

Claim 2 recites the limitation "the model excipient formulation" in line 1. There is insufficient antecedent basis for this limitation in the claim. It is unclear whether this recitation of a formulation is the same as what is provided in the providing step, choosing step, or measuring step of claim 1 or if this formulation is a different formulation.

Claims 12-14 recite the limitation "at least one membrane" in line 1. There is insufficient antecedent basis for this limitation in the claim. It is unclear whether this recitation of a membrane is the same as what is claimed in the measuring step of claim 1 or if this membrane is a different membrane.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejections of claims 1-5, 8, and 10-24 under 35 U.S.C. 103(a) as being unpatentable over Katz et al. [Journal of Pharmaceutical Sciences, 1965, volume 54, pages 591-594] in view of Tayar et al. [Journal of Pharmaceutical Science, volume 80, 1991, pages 590-598] in view of Loftsson et al. [Drug Development and Industrial Pharmacy, 1994, volume 20, pages 1699-1708] in view of Loftsson et al. [Drug Development and Industrial Pharmacy, 1997, volume 23, pages 473-481] in view of Lipinski et al. [Advanced Drug Delivery Reviews, volume 23, 1997, pages 3-25] are withdrawn in view of the arguments of applicant on pages 8-14 of the Remarks.

The rejections of claims 1 and 6-7 under 35 U.S.C. 103(a) as being unpatentable over Katz et al. in view of Tayar et al. in view of Loftsson et al. in view of Loftsson et al. (1997) in view of Lipinski et al. as applied to claims 1-5, 8, and 10-24 above, and further in view of Garcia-Ochoa et al. [Chemistry- A European Journal, 1999, volume 5, pp. 897-901] are withdrawn in view of the arguments of applicant on pages 14-15 of the Remarks.

The rejections of claims 1 and 8-9 under 35 U.S.C. 103(a) as being unpatentable over Katz et al. in view of Tayar et al. in view of Loftsson et al. in view of Loftsson et al. (1997) in view of Lipinski et al. as applied to claims 1-5, 8, and 10-24 above, and further in view of Colarusso et al. [Biophysical Journal; February 2002; volume 82, pages 752-761] are withdrawn in view of the arguments of applicant on pages 15-16 of the Remarks.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

35 U.S.C. 103 Rejection #1

Claims 1-5, 10-14, and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Loftsson [US Patent 5,324,718 issued 28 June 1994] in view of Lipinski et al. [Advanced Drug Delivery Reviews, volume 23, 1997, pages 3-25].

Claim 1 is drawn to a method of formulating a pharmaceutical composition comprising:

--comparing parameters of at least one pharmaceutical and a plurality of compounds, wherein the parameters consist of at least log(P) and molecular weight;

--based on the compared parameters, choosing at least one model compound from the plurality of compounds for each pharmaceutical, wherein the at least one model compound is different from the at least one pharmaceutical;

--providing at least one model compound-excipient formulation comprising at least one model compound and at least one excipient;

--measuring the diffusion of a model compound of at least one model compound-excipient formulation across at least one membrane;

--choosing a model compound-excipient formulation based on the measured model compound diffusion; and

--combining components comprising the at least one pharmaceutical and the at least one excipient of the chosen model compound-excipient formulation.

Claim 2 is dependent from claim 1 with the additional limitation that the model compound-excipient formulation is saturated in model compound.

Claim 3 is dependent from claim 1 with the additional limitation that the parameters further comprise the number of freely rotatable bonds.

Claim 4 is dependent from claim 1 with the additional limitation that the parameters further comprise the number of hydrogen bond donors and acceptors.

The invention of Loftsson studies cyclodextrin/drug complexation and states in the abstract:

> The invention provides a method for enhancing the complexation of a cyclodextrin with a lipophilic and/or water-libile drug, comprising combining from about 0.1 to about 70% (weight/volume) of a cyclodextrin and about 0.01 to about 5% (weight/volume) of a pharmaceutically acceptable, pharmacologically inactive, water soluble polymer in an aqueous medium with a lipophilic and/or water-labile drug to form a drug complex, optionally followed by removal of water. Related methods, co-complexes of drug/cyclodextrin/polymer, pharmaceutical compositions and cyclodextrin/polymer complexing agents are also provided.

Table 1 in column 15 of Loftsson lists pharmaceuticals and model compounds which bind to the cyclodextrins and parameters of solubility in five different solutions.

Table 3 in column 15 of Loftsson provided a model compound-excipient formulation comprising hydrocortisone and lists the solubility in cyclodextrin excipient at

various concentrations. Table 8 in column 18 of Loftsson lists the diffusivity across a cellophane membrane of the hydrocortisone (model compound)/cyclodextrin complex.

Through the data of the model compound of hydrocortisone in Table 8, pharmaceuticals such as those on Table 11 on columns 21-22 of Loftsson are better understood.

Loftsson, however, fails to teach the use of the specific parameters of molecular weight, Log(P) , and hydrogen bond donors and acceptors in assessing the parameters of the drugs.

The study of Lipinski et al. gives five rules for determining the solubility and potential for drugs in delivery. They are stated in column 1 of page 9 of Lipinski et al.:

> There are more than 5 H-bond donors (expressed as the sum of OHs and NHs);
> The MWT is over 500;
> The Lop P is over 5 (or MlogP is over 4.15);
> There are more than 10 H-bond acceptors (expressed as the sum of Ns and Os);
> Compound classes that are substrates for biological transporters are exceptions to the rule.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the invention of Loftsson by use of the rules of Lipinski et al. because simple substitution of one known element for another yields predictable results. Int his instant, simple substitution of the rules of Lipinski et al. for the guidance in Loftsson yields predictable results of better performing drugs that are more easily deliverable.

Claim 10 is dependent from claim 1 with the additional limitation that at least one model compound-excipient formulation comprises a plurality of different excipients. Table 5 in column 17 of Loftsson examines a plurality of cyclodextrin excipients.

Claim 11 is dependent from claim 1 with the additional limitation of utilizing a chemical reaction. The reaction of the model compound to the cyclodextrin to form a complex is a chemical reaction.

Claim 12 is dependent from claim 1 with the additional limitation that at least one membrane comprises a synthetic polymer membrane. Table 8 in column 18 of Loftsson lists the diffusivity across a cellophane membrane of the hydrocortisone (model compound)/cyclodextrin complex.

Claim 13 is dependent from claim 1 with the additional limitation that the at least one membrane comprises skin. Example 11 of Loftsson in columns 19-20 shows the absorbance of the cyclodextrin complexes on the skin of rabbit eyes.

Claim 14 is dependent from claim 1 with the additional limitation that the at least one membrane is selected from the group consisting of specific animal skins. Example 12 on column 20 of Loftsson explains the use of the cyclodextrins as mouthwash on human skin.

Claims 16-20 are dependent from claim 1 with the additional limitation of the model compound and pharmaceutical being experimentally and empirically determined. While the diffusivities in Table 8 of column 18 of Loftsson et al. are empirically calculated, molecular weight and structure are calculated parameters from the chemical names for model and pharmaceutical compounds.

35 U.S.C. 103 Rejection #2:

Claims 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Loftsson in view of Lipinski et al. as applied to claims 1-5, 10-14, and 16-20 in further view of Garcia-Ochoa et al. [Chemistry- A European Journal, 1999, volume 5, pp. 897-901].

Claims 6 and 7 are dependent from the drug formulation method of claim 1, wherein at least one model compound comprises a dye and the diffusion is monitored using fluorescence spectroscopy.

Loftsson in view of Lipinski et al. as applied to claims 1-5, 10-14, and 16-20 above fail to disclose any use of fluorescence or fluorescence spectroscopy.

The study of Garcia-Ochoa et al., entitled, "Probing hydrophobic nanocavities in chemical and biological systems with a fluorescent proton-transfer dye," teaches detecting cyclodextrins with fluorescent dyes for better visualization of excited-state intramolecular proton transfer (ESIPT) reactions (see bottom of column 1 on page 897).

The last sentence in the second paragraph of the methods on page 901 of Garcia-Ochoa et al. states, "^{1}H NMR spectra of 10^{-3}M solutions of HPMO [a fluorescent

dye] in D_2O in the absence and presence of 10^{-2}M β-CD [cyclodextrin] (almost saturated solution) were recorded at 500 MHz on a Varian Unity spectrometer at 303K..." The use of fluorescence and fluorescent spectroscopy is employed to detect the cyclodextrins.

It would have been obvious for someone of ordinary skill in the art at the time of the instant invention to combine Loftsson in view of Lipinski et al. as applied to claims 1-5, 10-14, and 16-20 and further in view of Garcia-Ochoa et al., for Garcia-Ochoa et al. is an extension of the cyclodextrin study with the use of fluorescence to more effectively monitor cyclodextrin concentration and location for purposes such as monitoring of ESIPT reactions.

35 U.S.C. 103 Rejection #3:

Claims 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Loftsson in view of Lipinski et al. in view of Garcia-Ochoa et al. as applied to claims 6-7 above, and further in view of Colarusso et al. [Biophysical Journal; February 2002; volume 82, pages 752-761].

Claim 8 is dependent from claim 6 with the additional limitation of the use of a plurality of diffusion cells.

Claim 9 is dependent from claim 6 with the additional limitation of the method of formulating a pharmaceutical composition of claim 1, but adds the limitation of recording an image of diffusion of a model compound.

Loftsson in view of Lipinski et al. in view of Garcia-Ochoa et al. as applied to claims 6-7 above, fail to record any images in their studies.

The article of Colarusso et al., entitled, "Reticulated lipid probe fluorescence reveals MDCK cell apical membrane topography," uses fluorescence and microscopy imaging techniques for a "more clear visualization of apical membrane features."

Colarusso et al. illustrates several fluorescent images of cells and the effects of cyclodextrins on them in Figures 1-4 and 6-7.

It would have been obvious for someone of ordinary skill in the art at the time of the instant invention to combine Loftsson in view of Lipinski et al. in view of Garcia-Ochoa et al. as applied to claims 6-7 above, and further in view of Colarusso et al. because Colarusso et al. use cyclodextrins and fluorescence in analyzing images of cells for a more clear illustration of cellular processes.

35 U.S.C. 103 Rejection #4:

Claims 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Loftsson in view of Lipinski et al. as applied to claims 1-5, 10-14, and 16-20 in further view of Loftsson et al. [Drug Development and Industrial Pharmacy, volume 20, 1994, pages 1699-1708].

Claim 21 is dependent from claim 1 with the additional limitation of incorporating the pharmaceutical composition into a transdermal delivery system.

Claim 22 is dependent from claim 21 with the additional limitation of contacting the pharmaceutical composition with the skin of a live mammal.

Claim 23 is dependent from claim 21 with the additional limitation that the transdermal delivery device comprised an adhesive patch.

Claim 24 is dependent from claim 1 with the additional limitation that the model compound-excipient formulation is incorporated into an adhesive patch.

Loftsson in view of Lipinski et al. as applied to claims 1-5, 10-14, and 16-20 above fail to disclose transdermal drug delivery.

Page 1700 of Loftsson et al., lines 21-24, states, "The molar substitution (MS) i.e. the average number of propylene oxide molecules that have reacted with one glucopyranose unit, was 0.6 or 0.9. HPβCD has a very good aqueous solubility (over 60% w/v) and forms stable complexes with many drugs." The HPβCD- hydrocortisone complex is chosen because of their compatibilities in size (i.e. the molecular weight of the hydrocortisone allows the molecule to fit into the cyclodextrin) and partitioning (i.e. the cyclodextrin is enabled to partition hydrophobically into the molecule). Hydrocortisone is not permeable into the body, but with the aid of the cyclodextrin excipient, is able to penetrate the body (i.e. transdermally). As stated in the abstract, "The influence of 2-hydroypropyl-β-cyclodextrin (HPβCD) on the permeability of hydrocortisone through semi-permeable cellophane membrane and hairless mouse skin was investigated."

In Loftsson et al. on page 1702, the sixth and seventh lines from the bottom of the page state, "Female hairless mice were killed by cervical dislocation, their full-thickness skins removed and placed in the previously described Franz diffusion cells." Thus Franz diffusion cells are used to measure diffusion across hairless mouse skin.

It would be obvious to someone of ordinary skill in the art at the time of the instant invention to modify Loftsson in view of Lipinski et al. as applied to claims 1-5, 10-14, and 16-20 in further view of Loftsson et al. because Loftsson et al. has the advantage of using transdermal drug delivery to improve the delivery of drugs through devices such as adhesive patches.

Response to Arguments

Applicant's arguments filed 12 July 2007 have been fully considered and they are persuasive. New grounds of rejection are applied.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Marjorie Moran, Supervisory Patent Examiner, can be reached at (571) 272-0720.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

9/25/07

RSN
25 September 2007

/Shubo (Joe) Zhou/
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PRIAMRY EXAMINER